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Prednisone and prednisolone bioavailability in renal transplant patients

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Prednisone and prednisolone bioavailability in renal transplant patients. Prednisone and prednisolone are drugs with the potential for therapeutic inequivalence due to bioavailability problems. The objective of our study was to compare the systemic bioavailability of prednisolone from oral prednisone and prednisolone. Nine kidney transplant patients receiving prednisone (12.5 to 22.5 mg per day) were administered, in a randomized fashion, the same dose of oral prednisone (Deltasone®), oral prednisolone (Delta-cortef®) and intravenous prednisolone (Hydeltrasol®). Prednisolone and prednisone levels were measured using a specific high-pressure liquid chromatographic assay. Since prednisolone exhibits dose-dependent pharmacokinetics because of nonlinear plasma protein binding, bioavailability was determined from unbound as well as total drug concentrations. Mean prednisolone bioavailability from oral prednisone and oral prednisolone, compared to the intravenous dose, was 84.5 ± 17.8% and 95.5 ± 17.6% using unbound drug concentrations and 86.1 ± 9.1% and 93.6 ± 9.2% determined from total drug concentrations. These differences were not statistically significant. Furthermore, no significant differences were observed between the two oral formulations in peak prednisolone levels, time of peak levels or half-life using either total or unbound drug concentrations. The results from our study indicate that both of the oral preparations tested provide similar bioavailability of active prednisolone and the conversion of prednisone to prednisolone occurs rapidly.

Biodisponibilité de la prednisone et de la prednisolone chez des transplantes renaux. La prednisone et la prednisolone sont des médicaments dont le potentiel thérapeutique peut différer en raison de problèmes de biodisponibilité. Le but de notre étude a été de comparer la biodisponibilité systémique de la prednisolone à partir de prednisone ou de prednisolone données per os. Neuf transplantés rénaux recevant de la prednisone (12,5 à 22,5 mg/jour) ont reçu de façon randomisée la même dose de prednisone (Deltasone®) orale, de prednisolone (Delta-cortef®) orale ou de prednisolone (Hydeltrasol®) intraveineuse. Les concentrations de prednisolone et de prednisone ont été déterminées avec un dosage spécifique utilisant une chromatographie liquide à haute pression. La prednisolone ayant une pharmacocinétique dose-dépendante en raison de la non linéarité de sa liaison aux protéines plasmatiques, sa biodisponibilité a été déterminée à partir de ses concentrations plasmatiques totale et libre. La biodisponibilité moyenne de la prednisolone à partir de prednisone ou de prednisolone orale, comparée à l'administration intraveineuse était de 84,5 ± 17,8% et 95,5 ± 17,6% à partir des concentrations libres et de 86,1 ± 9,1% et 93,6 ± 9,2% à partir des concentrations totales. Ces différences n'étaient pas significatives. De plus, il n'y avait pas de différences significatives entre les 2 préparations orales en ce qui concerne les pics de concentrations de prednisolone, l'heure de ces pics de concentrations ou la demi-vie, qu'on utilise les concentrations totales ou libres. Les résultats de notre étude indiquent que les deux préparations orales testées offrent une biodisponibilité de prednisolone active identique, et que la transformation de prednisone en prednisolone se produit rapidement.

Prednisone and prednisolone are synthetic glucocorticoid compounds commonly used in the treatment of a wide variety of disease states. Prednisone is assumed to be inactive and must be converted to the bioactive moiety prednisolone, which occurs via reduction of the 11-oxo group primarily by the liver enzyme, 11-β-hydroxydehydrogenase. In the absence of significant liver disease, the biotransformation of prednisone to prednisolone is usually rapid and extensive [1, 2]. In healthy subjects Rose, Yurchak, and Jusko [3] found the mean systemic bioavailability of prednisolone from oral prednisone to range from 85 to 99%. Some investigators have indicated that the administration of equal doses of either drug to normal subjects resulted in similar plasma prednisolone concentration-time profiles [4, 5]. However, other studies have demonstrated significantly higher peak prednisolone levels, larger areas under the plasma prednisolone concentration-time curve and greater prednisolone bioavailability following oral prednisolone compared with equivalent oral doses of prednisone [6–9]. Furthermore, it has been shown that a significantly greater variation exists in prednisolone bioavailability after oral prednisone dosing than after oral prednisolone dosing [6]. It has been suggested that if predictable plasma prednisolone concentrations are to be achieved, prednisolone should be used [6]. Some oral prednisone and prednisolone products may not be bioequivalent and drug substitution could result in important changes in the level of active prednisolone available. Thus formulation factors and possible differences in biotransformation determine the bioavailability of prednisolone from these orally administered corticosteroids.

The objective of our study was to determine the systemic bioavailability of prednisolone from a commonly used commercial formulation of prednisone and of prednisolone in kidney transplant patients. These patients are usually administered oral prednisone for immunosuppression. Bioavailability was assessed both in terms of total and unbound concentrations

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because the dose-dependent pharmacokinetics of prednisolone are primarily due to concentration-dependent plasma protein binding [3, 10–13].

Methods

Protocol. Nine clinically stable kidney transplant patients (six males, three females) ranging in age from 25 to 56 years (34 ± 10; mean ± SD) participated in our study, which was approved by the Committee on Human Research, University of California, San Francisco. Their weights ranged from 57 to 88 kg (72 ± 11) and six patients (nos. 2, 3, 4, 6, 7, 8) were clinically cushingoid. All patients were studied from 5 to 27 months following cadaver renal transplantation and had good to satisfactory kidney function with the serum creatinine ranging from 0.9 to 2.6 mg/dl (1.7 ± 0.5). Tests of liver function and serum albumin levels (range 4.1 to 4.6 g/dl) were in the normal range. All patients were taking a single daily maintenance dose of prednisone ranging from 12.5 to 22.5 mg. In addition, they were receiving azathioprine and various other drugs such as methyldopa, hydralazine, furosemide, propranolol, and vitamins.

Each patient was studied on three separate occasions in a randomized crossover design. On one occasion they received their usual oral dose (12.5 to 22.5 mg) of prednisone as Deltasone® (The Upjohn Company, Kalamazoo, Michigan) and on another the same oral dose of prednisolone as Delta-cortef® (The Upjohn Company). On the third occasion patients were administered an equivalent intravenous bolus dose of prednisolone as prednisolone sodium phosphate, Hydeltrasol® (Merck, Sharp and Dohme, West Point, Pennsylvania). Patients were fasted from midnight prior to the study day and for 4 hr after the dose the next morning. Venous blood samples, 10 ml each, were obtained from a heparin lock in a peripheral arm vein before the oral or intravenous doses and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hr after the dose. Additional samples were collected at 2.5, 5, and 10 min following the intravenous dose. Blood samples were collected in heparinized Vacutainer® blood collection tubes (stoppers removed) and immediately centrifuged; the plasma was removed and then frozen at −70° C until assayed.

Analytical methods and protein binding. Plasma concentrations of prednisolone, prednisone, cortisol, and cortisone were determined using a high-pressure liquid chromatographic assay [14]. This specific assay method allows the simultaneous measurement of these glucocorticoid compounds. The measurement limit for routine analysis is 5 ng/ml. The analytical recovery for all compounds is greater than 75%; the intraday variability is 1 to 3% (coefficient of variation) and the interday variability 3 to 10% (coefficient of variation).

The plasma protein binding of prednisolone was determined by equilibrium dialysis. Due to the nonlinear concentration-dependent binding of prednisolone the protein binding of all plasma samples from each patient were determined. Acrylic plastic equilibrium dialysis cells (Technilab®) with a 1-ml maximum capacity per cavity were used. The membrane used was Spectrapor® No. 2 (Spectrum Medical Industries, Queens, New York) with a molecular weight cutoff of 12000 to 14000. One-half ml of plasma is equilibrated against 0.5 ml of isotonic Krebs-Ringer buffer (pH 7.4; 0.153 M) containing [6,7 (n)-^{3}H] prednisolone (9 ng/ml; specific activity 43 Ci/mmoles; 96 to 99% radiochemical purity; Amersham, Arlington Heights, Illinois). In addition, the purity of the radiolabeled prednisolone was confirmed in our laboratory prior to use by thin-layer chromatography and found to be 98% pure. The amount of labeled prednisolone used was included in all calculations of protein binding. Equilibrium was reached at 16 hr in a Dubnoff® Metabolic Shaking Incubator, at a water temperature of 37° C. One-tenth ml of dialyzed plasma and 0.1 ml of dialyzed buffer were then transferred to individual glass scintillation vials to which is added 10 ml Aquasol® (New England Nuclear, Boston, Massachusetts). After being shaken, the vials were counted on a Packard Liquid Scintillation Spectrometer (Model 3320). The counts per minute of the plasma and buffer samples are converted to disintegrations per minute using the channels-ratio method of quench correction. Additional correction was made for background counts. Less than 2% of the radioactivity was bound to the dialysis membrane and/or cell surfaces. Plasma samples containing prednisolone (387 to 6720 ng/ml) analyzed after equilibrium dialysis by both radiochemical assay and HPLC assay indicated similar results for the percent of the prednisolone bound to plasma proteins [13]. The coefficient of variation for paired observations was 6.1%. Thus the radiolabeled compound did not give erroneous results after the equilibration period, and all subsequent protein binding studies were carried out using radioactivity measurements. Prednisolone is stable in the dialysis cells during the equilibration period. Furthermore, the presence of heparin in plasma at both low (14 U/ml) and high (100 U/ml) concentrations does not alter the protein binding of prednisolone compared to serum (containing no heparin), over varying prednisolone concentrations up to 5000 ng/ml. Calculations of the bound and unbound drug concentrations postdialysis were made with corrections for the shifts of drug and volume changes occurring during the dialysis procedure (Tozer, Gambertoglio, Furst, Avery, and Holford, to be published). This correction is necessary in equilibrium dialysis studies because of the increase in the plasma volume side relative to buffer volume side postdialysis which causes a decrease in plasma bound and unbound drug concentrations. Furthermore, prednisolone concentrations on the plasma side decrease due to diffusion from plasma into buffer during the dialysis. Thus at equilibrium the concentration of total prednisolone in plasma is lower than that obtained from the patient and measured by HPLC; and thus, the fraction unbound corresponds to this lower total drug concentration. The concentrations of unbound (P_u) and bound (P_{bnd}) drug postdialysis were then calculated for each plasma sample.

Data analysis. (1) Protein binding: Prednisolone binding to plasma protein is nonlinear and may be described by the function [3, 15–18]:

$$P_{bnd} = (CAP_1 \cdot P_u) \div (KD_1 + P_u) + S \cdot P_u \quad \text{Eq. 1}$$

where CAP_1 and KD_1 are the binding capacity and dissociation constant of a saturable binding site (transcortin), and S is the ratio of capacity to dissociation constant (CAP_2/KD_2) of a nonsaturated binding site (albumin). Once estimates of the binding parameters, CAP_1, KD_1, and S for prednisolone are obtained from each patient's study the unbound concentration is derived from equation 2. That is:

$$P_u = \left(B + \sqrt{B^2 + 4\,A\,KD_1\,P_{tot}}\right) \div A \quad \text{Eq. 2}$$

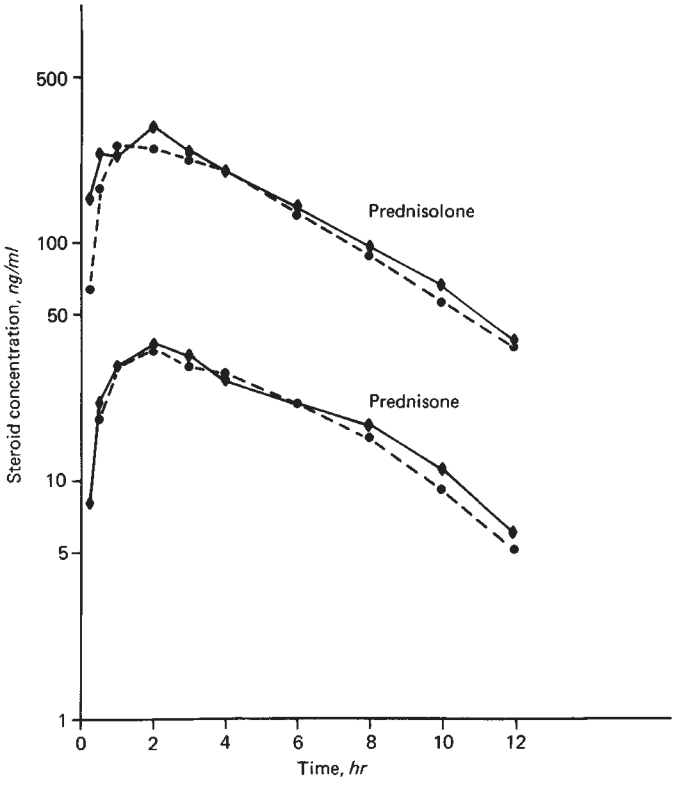

Fig. 1. *Total plasma concentrations of prednisolone and prednisone in patient 9 following the administration of 15 mg oral prednisone* (● - - - - ●) *and 15 mg oral prednisolone* (◆——◆).

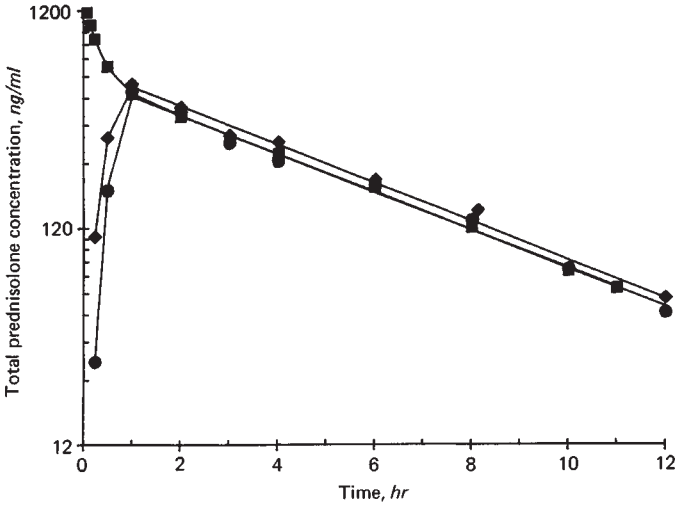

Fig. 2. *Total plasma prednisolone concentrations in patient 8 following the administration of 22.5 mg of intravenous prednisolone,* (■ —— ■), *oral prednisolone,* (◆ —— ◆), *and oral prednisone* (● —— ●).

where P_{tot} is total plasma concentration in vivo, $B = (P_{tot} - CAP_1 - A)$ and $A = 1 + S$. This equation relates the total concentration of prednisolone measured in the patient (that is, before equilibrium dialysis) to the concentration of unbound drug in that same patient's sample. Protein binding parameters were estimated using unweighted nonlinear least squares regression [19].

(2) Pharmacokinetics: A two-compartment model was used to describe plasma concentrations. Bolus input was used for intravenous doses and zero-order absorption with lag time for oral doses. Observed concentrations were weighted by the reciprocal of the value squared. Half-life was calculated by dividing 0.693 by the elimination rate constant. The area under the plasma concentration time curve (AUC) was obtained using the log-trapezoidal rule and the remaining AUC beyond the last measured data point was estimated by dividing the predicted value for the last data point by the terminal disposition rate constant estimated from the pharmacokinetic model. The systemic bioavailability of prednisolone from the oral prednisolone doses was calculated from the ratio of the area under the curve of prednisolone after the oral steroid dose to the area under the curve from the intravenous prednisolone. Plasma clearance (CL) and volume of distribution at steady-state (Vss) were calculated using the two-compartment model parameter estimates in the following expressions:

$$CL = V_1 \frac{\alpha\beta}{K_{21}} \text{ and } Vss = V_1 [(K_{21} + K_{12}) \div (K_{21})]$$

Eqs. 3 and 4

where V_1 is the volume of the central compartment; α and β are the initial and terminal disposition rate constants; and K_{12} and K_{21} are the intercompartmental distribution rate constants. Compartment-independent estimates of CL and Vss were calculated using:

$$CL = \frac{\text{Dose}}{\text{AUC}} \text{ and } Vss = [\text{Dose (AUMC)}] \div (\text{AUC})^2$$

Eqs. 5 and 6

where AUMC is the area under the first moment of the plasma concentration-time curve using the log-trapezoidal rule [20, 21]. The pharmacokinetic parameters describing the disposition of prednisolone based on total and free drug plasma concentrations were estimated by non-linear least squares regression [22]. Prednisone half-life was estimated using log-linear regression when at least four points on the terminal linear portion of the plasma curve had been measured.

Statistical analysis. Statistical comparisons between pharmacokinetic parameters were made using Student's paired *t* test and Wilcoxon's sign rank test for paired data on the PROPHET computer system [23]. Both tests were applied to all comparisons and a statistically significant difference was defined as $P < 0.05$. Results are reported as mean ± SD.

Results

The bioavailability characteristics of oral prednisone and oral prednisolone were made by comparing peak prednisolone concentrations, time of peak levels, half-life and bioavailability of prednisolone compared to an intravenous dose of prednisolone.

Figure 1 shows total plasma prednisolone and prednisone concentrations in patient 9 following oral prednisone and oral prednisolone administration. After either oral steroid dose, similar plasma concentrations of prednisolone and prednisone were observed, demonstrating the rapid interconversion of the two steroids. Prednisolone bioavailability was 81 and 88% from oral prednisone and oral prednisolone, respectively. On the

Table 1. Prednisolone bioavailability data from oral prednisone and oral prednisolone[a]

Patient no.	Steroid dose *mg*	Weight *kg*	Total prednisolone concentration								Unbound prednisolone concentration					
			Peak Time *hr*		Peak concentration *ng/ml*		Half-life *hr*		Systemic [b] bioavailability %		Peak concentration *ng/ml*		Half-life *hr*		Systemic bioavailability %	
			P	P_o	P	P_o	P	P_o	P	P_o	P	P_o	P	P_o	P	P_o
1	15	78	1.0	3.0	228	262	3.2	3.1	81.3	100.3	43	51	2.7	2.4	69.4	88.9
2	15	76	0.5	1.0	550	452	3.3	3.2	92.8	87.7	150	82	2.3	2.4	103.8	79.9
3	17.5	82	0.5	1.0	455	332	3.8	4.3	103.7	110.7	100	80	2.9	3.4	110.4	129.3
4	15	75	2.0	2.0	282	272	3.4	3.3	78.0	87.7	57	54	2.8	2.8	69.2	81.8
5	15	70	2.0	2.0	212	237	3.5	2.6	94.5	81.0	24	42	3.2	2.0	65.9	72.3
6	12.5	58	1.0	1.0	315	371	3.8	3.5	85.1	102.5	61	104	2.9	2.6	67.6	94.5
7	12.5	88	0.5	0.5	246	292	2.9	3.2	75.4	91.5	50	61	2.4	2.8	81.1	111.6
8	22.5	57	1.0	1.0	508	556	3.4	3.4	82.6	92.7	101	146	2.4	2.3	89.2	99.5
9	15	60	1.0	2.0	258	308	3.5	3.4	81.3	88.1	54	58	2.7	2.6	103.5	101.5
Mean			1.1	1.5	339	342	3.4	3.3	86.1	93.6	71	75	2.7	2.6	84.5	95.5
SD			0.6	0.8	129	103	0.3	0.5	9.1	9.2	39	33	0.3	0.4	17.8	17.6

[a] No significant differences were observed between prednisone and prednisolone, using Student's paired *t* test and Wilcoxon's sign rank test.
[b] Systemic availability is relative to an intravenous dose of prednisolone.
Abbreviations are P, oral prednisone; P_o, oral prednisolone.

average prednisolone concentrations were 8 to 20 times the corresponding prednisone levels after administration of either oral steroid product. The half-life of prednisone averaged 4.6 ± 0.9 hr (N = 4) and 4.8 ± 0.5 hr (N = 4) following oral prednisone and oral prednisolone, respectively.

Table 1 shows the results from total drug concentration measurements. Peak prednisolone levels were found in the 0.5- to 2-hr samples (except for patient 1 whose peak level occurred at 3 hr after oral prednisolone) and were of similar magnitude for each patient after either oral prednisone or oral prednisolone. Plasma prednisolone concentrations were readily measurable even in the blood samples obtained 15 min after either drug was administered. Thus, the conversion of prednisone to its active metabolite prednisolone occurs very rapidly. There were no significant differences in the mean half-life of plasma prednisolone when comparing oral prednisone and oral prednisolone. Based on total drug plasma concentrations the average bioavailability of prednisolone from oral prednisone and oral prednisolone was 86.1 ± 9.1% and 93.6 ± 9.2%, respectively. Figure 2 illustrates total plasma prednisolone concentrations in patient 8 after the same dose of oral prednisone, oral prednisolone, and intravenous prednisolone. For the oral doses peak levels occurred at the same time, and there is a close similarity in plasma levels achieved. In this patient the bioavailability of prednisolone was approximately 83% from oral prednisone and 93% from oral prednisolone.

Estimates of the protein binding parameters for prednisolone determined from the intravenous doses, were CAP_1, 167.87 ± 52.04 ng/ml; KD_1, 17.95 ± 5.77 ng/ml and S, 2.06 ± 0.88. The bioavailability data for the two oral steroid preparations determined from unbound prednisolone concentrations are shown in Table 1. The mean time of peak concentrations are the same as seen with total drug concentration measurements. However, with regard to peak concentrations there is a larger difference between the two doses for some patients. For example, in patients 5 and 6 the peak prednisolone concentration from the oral prednisone is approximately 60% of that from oral prednisolone when based on unbound drug levels. In contrast, when based upon total prednisolone concentrations the differences between the two compounds is less; the peak concentration from oral prednisone measuring 90% of that from oral prednisolone. The elimination half-life of prednisolone estimated from unbound drug concentrations was very similar between the two products, and mean values were not significantly different. The absolute bioavailability of prednisolone estimated from unbound drug concentrations was not significantly different between the two formulations. Average values were 84.5 ± 17.8% and 95.5 ± 17.6% for oral prednisone and oral prednisolone, respectively. The mean values for each preparation determined from unbound drug concentrations were very close to the mean values based on total drug concentrations; however, the standard deviation was twice as great. In some cases, the actual values for absolute bioavailability were quite different when comparing estimates based on total or free drug concentrations. For example, in patient 5 the prednisolone bioavailability from oral prednisone measured 95% when total drug concentrations were used and only 66% when free concentrations were used. Furthermore, in this patient bioavailability is greater after oral prednisone compared to oral prednisolone when total drug measurements are used and the reverse is true when unbound concentrations are used. Figure 3 shows the concentrations of unbound prednisolone in patient eight. Peak concentrations were higher after oral prednisolone and prednisolone availability was 89% and 100% from oral prednisone and prednisolone, respectively.

Comparison of prednisolone bioavailability between the cushingoid and noncushingoid patients revealed no significant differences between the two groups.

Table 2 lists the pharmacokinetic parameters of unbound prednisolone following intravenous prednisolone in these patients. The mean systemic clearance of unbound drug was approximately 12 ml/min·kg and the steady-state volume of

Table 2. Pharmacokinetic parameters of unbound prednisolone from intravenous prednisolone

Patient no.	CL *ml/min·kg*		Vss *liter/kg*		t½,α *min*	t½,β *hr*
	2CM	CI	2CM	CI		
1	11.0	10.8	2.1	2.0	5.4	2.4
2	8.8	8.8	1.8	1.8	3.6	2.7
3	11.2	11.0	2.0	1.9	7.8	2.4
4	10.8	10.0	2.0	1.8	4.9	2.4
5	14.1	13.9	2.2	2.2	5.2	2.1
6	9.3	9.1	1.8	1.7	4.7	2.3
7	10.8	10.6	2.2	2.2	3.4	2.5
8	14.7	14.5	2.8	2.7	11.1	2.5
9	14.2	13.9	3.1	3.1	5.1	2.8
Mean	11.7	11.4	2.2	2.2	5.7	2.5
SD	2.2	2.2	0.4	0.5	2.4	0.2

Abbreviations are CL, plasma clearance; Vss, volume of distribution at steady-state; t½, α, initial disposition half-life; t½, β, terminal disposition half-life; 2CM, calculated using two-compartment model equations; CI, calculated using compartment-independent equations.

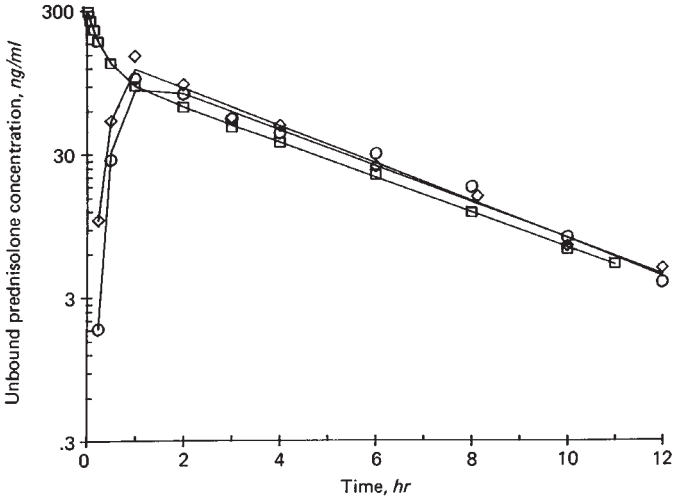

Fig. 3. *Unbound plasma prednisolone concentrations in patient 8 following the administration of 22.5 mg of intravenous prednisolone,* (□ ——— □), *oral prednisolone,* (◇ ——— ◇), *and oral prednisone* (○ ——— ○).

distribution 2 liters/kg. The terminal half-life averaged 2.5 hr, similar to that seen from the oral prednisone and prednisolone doses.

Only one patient (no. 1) had plasma concentrations of cortisol higher than 10 ng/ml up to the first hour of blood sampling, which was observed in both the oral and intravenous studies. In the remainder of the patients cortisol concentrations were unmeasurable.

Discussion

Prednisone and prednisolone products have been identified as drugs with a potential for therapeutic inequivalence because of bioavailability problems [24, 25]. This was suggested by poor aqueous solubility and cases of therapeutic failure due to poor absorption [26–28]. Although oral prednisone is used more commonly than oral prednisolone, the two compounds are generally believed to be therapeutically equivalent and interchangeable.

Early studies [4, 5] found that the oral administration of the same dose of prednisone and prednisolone to normal subjects resulted in similar prednisolone concentrations. Davis et al [6] found peak prednisolone concentrations after a 10 mg oral dose to normal subjects to be significantly higher following prednisolone than after prednisone being 115.8 ± 22.8 ng/ml and 95.9 ± 27.3 ng/ml, respectively. Areas under the plasma prednisolone-time curve (AUC) were greater after prednisolone than after prednisone although the difference was not significant owing to the large scatter in AUC after prednisone. Prednisolone bioavailability after prednisolone ranged from 22 to 127% (mean 78%) of that observed after prednisolone (determined as AUC after prednisone/AUC after prednisolone). They [6] concluded that if predictable plasma prednisolone concentrations are to be achieved, prednisolone should be used rather than prednisone. Tse and Welling [7] studied a single healthy subject after the same oral dose of prednisolone and prednisone and observed plasma prednisolone profiles to be similar after each drug but much higher during the first 4 hr after prednisolone. The prednisolone AUC following oral prednisone was 75% of that after oral prednisolone.

Meikle, Weed, and Tyler [8] administered oral prednisone and an equivalent dose of intravenous prednisolone to normal subjects and determined that 69 ± 12% of oral prednisone was absorbed and metabolized to prednisolone. Subsequently Petereit and Meikle [9] administered prednisolone orally and intravenously to normals and found the bioavailability of prednisolone higher than in their study with oral prednisone being 82 ± 13% with a range of 60 to 92%.

The purpose of our study was to compare in kidney transplant patients the bioavailability of prednisolone from oral prednisone and oral prednisolone relative to an intravenous dose of prednisolone. In addition, we were able to estimate prednisolone bioavailability using both total and unbound drug concentrations. Because the binding of prednisolone changes with concentration, estimates of clearance based on total drug concentrations are misleading because they are confounded by the variation in binding. We believe that using unbound drug concentrations are more appropriate for prednisolone bioavailability studies. During the intravenous studies where the highest plasma concentrations are obtained, the unbound fraction averaged 28% at the highest concentrations and declined to 9% at the lowest concentrations. In a study of healthy subjects by Rose, Yurchak, and Jusko [3] clearance (Dose/AUC), as well as steady-state volume of distribution based on unbound drug concentrations exhibited no significant differences in relation to dose after 5, 20, and 40 mg of prednisolone given intravenously. However, when these pharmacokinetic parameters were determined from total drug concentrations, significant increases occurred with increasing dose. Because one of the basic assumptions in the calculation of bioavailability is that clearance remains constant [29], the use of unbound drug concentrations appear to be the most suitable.

An interesting finding was the larger intersubject variability in unbound drug bioavailability compared to that based on total

prednisolone concentrations (Table 1). The reason for this is unknown; however, it has been observed previously [18].

Estimates of the pharmacokinetic parameters for unbound prednisolone in our patients (Table 2) were similar to those observed in healthy subjects administered 5, 20, and 40 mg of intravenous prednisolone [3]. Mean values for unbound drug were reported to range from 828 to 1050 ml/min/1.73 m^2 for plasma clearance; 117 to 168 liters/1.73 m^2 for steady-state volume of distribution; and 1.7 to 2.2 hr for half-life. The estimation of prednisolone half-life based on unbound drug concentrations is shorter than that observed from total drug concentrations due to the non-linear plasma protein binding [30, 31].

In conclusion, no significant differences were observed in mean values between the two oral formulations tested whether based on total or unbound drug concentrations. However, it is important to note that seven of nine patients had greater absolute systemic bioavailability (range 6 to 30%) of prednisolone from prednisolone tablets using unbound drug data. Obviously, the results of any study of this type are somewhat dependent on the commercial preparation being utilized and specific formulation factors which might affect bioavailability. The results of our study indicate that both of the oral preparations tested, prednisone and prednisolone, provide similar bioavailability of active prednisolone. Furthermore, the conversion of prednisone to prednisolone occurs rapidly in these patients. Thus kidney transplant patients should obtain approximately the same effect and be able to receive either oral corticosteroid for immunosuppressive therapy.

Acknowledgments

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